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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/508,860

09/24/2004

Mitsuru Sakai

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SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC 20037

EXAMINER

GAKH, YELENA G

ART UNIT

PAPER NUMBER

1797

MAIL DATE

DELIVERY MODE

02/26/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/508,860	Applicant(s) SAKAI ET AL.	
	Examiner Yelena G. Gakh, Ph.D.	Art Unit 1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 January 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-8 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>09/24/04, 01/27/05, 05/07/07</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Preliminary amendment filed on 01/27/05 is acknowledged. Claims 1-8 are pending in the application.

Information Disclosure Statement

2. IDS filed on 09/24/04 is not accompanied with the references; only the most pertinent reference of Buchholz is considered and provided along with PTO-892 form.

Claim Objections

3. Claims 1-8 are objected to because of the following informalities: the claims are written not in accordance with the US practice. The examiner suggests deleting the words "being characterized by" in claim 1 and changing the expressions "characterized in that" with the word "wherein" in dependent claims, e.g. claim 2: "the method for assaying Coenzyme A molecules according to claim 1, wherein the step of extracting the Coenzyme A molecule from the biological sample comprises a step of agitating a freeze-shattered biological sample in a perchloric acid solution and a step of subjecting the supernatant to centrifugation separation".

The examiner suggests amending other claims in a similar manner.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 2 recites the term "freeze-shattered"; it appears that this is not a conventional term in the art; the term should be either explained or substituted with a conventional term.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

Art Unit: 1797

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. **Claims 1-6** are rejected under 35 U.S.C. 103(a) as being unpatentable over Buchholz et al. (Anal. Biochem., 2001) (Buchholtz) in view of Hosokawa et al. (Anal. Biochem., 1986) (Hosokawa).

Buchholz teaches "quantification of intracellular metabolites in *Escherichia coli* K12 using liquid chromatographic-electrospray ionization tandem mass spectrometric techniques" (Title), including assaying concentrations of Coenzyme A molecules (acetyl-CoA). The method comprises adding cGMP as an internal standard to the cell pellets, adding perchloric acid, storing cells at -80°C, centrifuging and neutralizing the supernatant and performing HPLC-ESI-MS-MS analysis (Abstract and .

Buchholz does not specifically disclose a step of solid phase extraction of the sample and using a structural analog of the coenzyme A as an internal standard.

Hosokawa teaches "determination of short-chain acyl-coenzyme A esters by high-performance liquid chromatography" with esters obtained from tissue. The method comprises extraction from freeze-clamped rat livers with perchloric acid, applying the extract to Sep-Pak

C18 cartridge (solid phase extraction with octadecylsilyl group) and eluting the extract with ethanol/water containing ammonium acetate. The eluate is separated by HPLC using reverse-phase columns with linear gradient of acetonitrile. Isobutyryl-CoA is used as an internal standard (Claim 6) (Abstract).

It would have been obvious for a person of ordinary skill in the art to apply the step of solid phase extraction of the coenzymes with experimental conditions taught by Hosokawa to Buchholz' method, because it allows a better separation of such analogous compounds as malonyl-CoA, succinyl-CoA, acetyl-CoA, acetoacetyl-CoA, and propionyl-CoA, as indicated by Hosokawa (see Abstract).

9. **Claims 7 and 8** are rejected under 35 U.S.C. 103(a) as being unpatentable over Buchholz in view of Hosokawa, as applied to claims 1-6 above, and further in view of Reszko et al. (Anal. Biochem., 2001, IDS) (Reszko).

Buchholz in view of Hosokawa do not specifically teach substituting at least three of the carbons of the main carbon chain in CoA analog with ^{13}C .

Reszko teaches "assay of the concentration and ^{13}C -isotopic enrichment of malonyl-coenzyme A by gas chromatography-mass spectrometry", comprising perchloric acid extraction of the tissue, spiking the extract with $[\text{U-}^{13}\text{C}_3]\text{malonyl-CoA}$ or dimethylmalonyl-CoA internal standard and isolation of short-chain acyl-CoA fraction on an oligonucleotide purification cartridge (Abstract).

It would have been obvious for a person of ordinary skill in the art to introduce the step of ^{13}C -isotopic enrichment of coenzyme A ester analog into Buchholz-Hosokawa's method, because it allows investigating the origin of the acetyl moiety of malonyl-CoA using mass spectrometry, as indicated by Reszko (page 69, right column).

Reszko further indicates that "in lipogenic organs, a minimum value of the turnover of malonyl-CoA can be estimated from the rate of fatty acid syntheses measured by the incorporation of ^2H or ^3H from deuterium- or tritium-enriched water", which makes it obvious for a person of ordinary skill in the art to use deuterium-enriched internal standard instead of ^{13}C -enriched internal standard, because it is useful for analysis of malonyl-CoA from lipogenic organs and is much easier to obtain than ^{13}C -enriched standards.

Conclusion

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. *Hellerstein (US 5,338,686)* teaches "a method for determining acetyl-coenzyme A (acetyl -CoA) mass isotope enrichment in a human subject" using mass spectrometry; *Chait et al. (US 6,391,649)* teach "a method for the comparative quantitative analysis of proteins and other biological material by isotopic labeling and mass spectrometry" including MS analysis of CoA; *Deutsch et al. (Anal. Biochem., 1994)* teach "isolation and quantitation of long-chain acyl-coenzyme A esters in brain tissue by solid-phase extraction" (Title); *Larson et al. (The Plant Journal, 2001)* teach "a novel technique for the sensitive quantification of acyl CoA esters from plant tissue". The closest art, which is not a prior art for the instant application: *Hayashi et al. (Biosci. Biotechnol. Biochem., 2006)* teach "Determination of acetyl-CoA and malonyl-CoA in germinating rice seeds using the LC-MS/MS technique"; *Minler et al. (Anal. Biochem., 2006)* teach "quantification of malonyl-coenzyme A in tissue specimens by high-performance liquid chromatography/mass spectrometry".

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Yelena G. Gakh/
Primary Examiner, Art Unit 1797

2/17/2008